STATISTICAL ANALYSIS PLAN

Study Protocol Number:	E2006-A001-102
Study Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Evaluate the Respiratory Safety of Lemborexant in Adult and Elderly Healthy Subjects and Adult and Elderly Subjects with Mild Obstructive Sleep Apnea
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2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
ATC	anatomical therapeutic class
BMI	body mass index
CI	confidence interval
CRF	case report form
CSR	clinical study report
E2006	lemborexant
ECG	electrocardiogram
FAS	full analysis set
HV	healthy volunteer
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini Mental State Examination
OSA	obstructive sleep apnea
PBO	Placebo
PD	pharmacodynamic
PK	pharmacokinetic
PSG	Polysomnography
SAE	serious adverse event
SAP	statistical analysis plan
SD	Standard deviation
SI	Système International
SOC	system organ class
TEAE	Treatment-emergent adverse event
TLG	tables, listings, and graphs
WHO	World Health Organization

3 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for Eisai Protocol E2006-G000-102 (for both cohort 1 and cohort 2). Cohort 1 comprises the healthy volunteer subjects (HV) and cohort 2 comprises the subjects with obstructive sleep apnea (OSA). Additional exploratory or post-hoc analyses not identified in this SAP may be performed to facilitate interpretation of study results and documented in the clinical study report.

This document is prepared on the basis of the final study protocol version 8.0 (dated 11 Dec 2017). The reader is referred to the study protocol, the case report form (CRF), general CRF completion guidelines, and various data collection instruments employed in the study for details of study design, conduct, and data collection.

This SAP is to be reviewed and approved prior to study database lock. If any updates are made upon blinded review of study data or for any other reasons in the course of the study, such modifications and rationale are likewise to be documented and approved prior to unblinding of study database.

3.1 Study Objectives

3.1.1 Primary Objectives

Primary Objective (Healthy Volunteer [HV] Cohort)

To determine whether lemborexant decreases the peripheral oxygen saturation (SpO_2) during total sleep time (TST) in healthy adult and elderly subjects after a single dose of treatment compared with placebo

Primary Objective (Obstructive Sleep Apnea [OSA] Cohort)

To determine whether lemborexant increases the AHI after multiple doses of treatment in adult and elderly subjects with mild OSA compared with placebo

3.1.2 Secondary Objectives

Secondary Objectives (HV Cohort)

1. Determine whether lemborexant increases the apnea-hypopnea index (AHI) after a single dose of treatment compared with placebo
2. Determine whether lemborexant decreases SpO_2 during TST velow defined thresholds after a single dose of treatment compared with placebo
3. Evaluate safety and tolerability of lemborexant

Secondary Objectives (OSA Cohort)

1. Determine whether lemborexant increases the AHI after the first dose of treatment compared with placebo
2. Determine whether lemborexant decreases the mean SpO_2 during TST after the first and multiple doses of treatment compared with placebo

3. Determine whether lemborexant increases the proportion of TST during which the SpO_2 is decreased below defined thresholds after the first and multiple doses of treatment compared with placebo
4. Evaluate safety and tolerability of lemborexant

3.1.3 Exploratory Objectives (HV and OSA Cohorts)

Explore the effects of lemborexant compared with placebo after a single dose in HV Cohort and after the first and multiple doses in the OSA Cohort on the following:

5. The mean SpO_2 during rapid eye movement (REM) sleep, non-REM (NREM) sleep, and wake
6. AHI during REM and NREM sleep
7. AHI separately for adult and elderly subjects
8. The mean SpO_2 during TST separately for adult and elderly subjects

In addition, explore the following for both HV and OSA Cohorts:

1. Plasma concentrations of lemborexant and metabolites M4, M9 and M10.
2. Exposure-response (E-R) relationships between lemborexant concentrations and pharmacodynamic (PD) variables, including but not limited to respiratory safety variables (AHI, mean SpO_2 during TST, proportion of TST during which the SpO_2 is decreased below defined thresholds)

3.2 Overall Study Design and Plan

HV Cohort

The HV Cohort comprises a randomized, double-blind, placebo-controlled, 3-period crossover study.

Eligible healthy adult and elderly subjects will be randomized to treatment sequence A, B or C, each consisting of 3 Treatment Periods, each of one night's duration, in which subjects will receive a single dose of lemborexant 10 mg, or lemborexant 25 mg, or placebo; Treatment Periods will be separated by a washout interval of at least 14 days. A sufficient number of subjects will be randomized to ensure that 8 evaluable adult subjects (<65 years) and 4 evaluable elderly subjects (≥65 years) complete the study.

Treatment Sequence	**Treatment Periods in the HV Cohort**		
	1 (one night)	**2 (one night)**	**3 (one night)**
A	lemborexant-matched placebo	lemborexant 10 mg	lemborexant 25 mg
B	lemborexant 10 mg	lemborexant 25 mg	lemborexant-matched placebo
C	lemborexant 25 mg	lemborexant-matched placebo	lemborexant 10 mg

OSA Cohort

The OSA Cohort comprises a randomized, double-blind, placebo-controlled, 2-period crossover study.

Adult and elderly subjects with mild OSA will be randomized to treatment sequences D or E, each consisting of 2 Treatment Periods, each of 8 nights' duration, in which subjects will receive lemborexant 10 mg or placebo. The Treatment Periods will be separated by a washout interval of at least 14 days. A sufficient number of subjects will be randomized to ensure that 20 evaluable adult subjects (<65 years) and 10 evaluable elderly subjects (≥65 years) complete the study.

Treatment Sequence	Treatment Periods in the OSA Cohort	
	1 (eight nights)	2 (eight nights)
D	lemborexant-matched placebo	lemborexant 10 mg
E	lemborexant 10 mg	lemborexant-matched placebo

Phases of the Study (HV and OSA Cohorts)

For both the HV and OSA cohorts, there will be 2 phases, Prerandomization and Randomization. The Prerandomization Phase for both cohorts will consist of the Screening Period (up to 21 days) and a Baseline Period (≤1day prior to randomization).

For the HV Cohort, the Randomization Phase will comprise 3 Treatment Periods, each of 1-day duration, separated by a washout interval of at least 14 days, followed by a 14-day Follow-Up Period.

For the OSA Cohort, the Randomization Phase will comprise 2 Treatment Periods, each of 8 days duration, separated by a washout interval of at least 14 days, and a Follow-Up Period of 14 days.

For both cohorts, an End of Study (EOS) Visit will occur at least 14 days after the final dose of study medication.

4 DETERMINATION OF SAMPLE SIZE

Sample Size Rationale

HV Cohort:

A mean difference of 5 percentage points between treatments in SpO_2 is considered to be clinically meaningful in a study of the respiratory safety of suvorexant in healthy adult volunteers (Uemura, et al., 2015). From that source, the within-subject variance is assumed to be 0.315%. With a total of 12 subjects (4 elderly and 8 adults) completing the study and assuming that the true difference between treatments is -1.0, there is 99% power that the lower bound of the 90% confidence interval for the difference in SpO_2 (lemborexant - placebo) would be greater than -5. Although the estimate of within-subject variability is based on a study of adult healthy volunteers, the addition of elderly subjects is expected to have a minimal effect on the combined variability and thus a minimal effect on the power.

OSA Cohort: A mean difference between treatments in AHI > 5 is considered clinically meaningful in studies of the respiratory safety of sleep agents in OSA (Kryger, et al., 2007, Sun, et el., 2016). The within-subject variance is assumed to be 25.34 for AHI for adult subjects (Sun, et al, 2016) and 30.41 for AHI for elderly subjects (where the elderly within-subject variance is estimated from adult data + 20%, Mitterling, et al, 2015; Lee, et al, 2016). Assuming the true difference in AHI (lemborexant – placebo) on Day 8 is as high as 1.5, a total of 30 subjects completing the study (20 adult, 10 elderly), provides 82% power that the upper bound of the 90% CI for the treatment difference in AHI (lemborexant − placebo) on Day 8 would be < 5.

Sample Size Estimates for OSA Cohort

Description	Combined within-subject variance of AHI	Adult N	Elderly N	Total N	Total Power (%)
80% overall power with 20 adult subjects	26.96	20	10	30	82
85% overall power with 20 adult subjects	27.38	20	14	34	86
80% overall power with 20 elderly subjects	28.54	12	20	32	82
85% overall power with 20 elderly subjects	28.16	16	20	36	86
Equal number of subjects	27.875	20	20	40	90

5 STATISTICAL METHODS

All analysis will be reported separately for each cohort. All descriptive statistics for continuous variables will be reported using mean, standard deviation (SD), median, minimum and maximum. Categorical variables will be summarized as number (percentage) of subjects.

All statistical tests will be based on the 5% level of significance (2-sided), unless otherwise stated. If statistical comparisons are not defined, all pairwise comparisons will be tested.

5.1 Study Endpoints

5.1.1 Primary Endpoints

Primary Endpoint (HV Cohort)

The mean SpO_2 during TST on Day 1 of treatment

Primary Endpoint (OSA Cohort)

The AHI on Day 8 of treatment

5.1.2 Secondary Endpoints

Secondary Endpoints (HV Cohort)

1. The AHI on Day 1 of treatment
2. The percentage of TST during which SpO_2 is <90%, <85% and <80% on Day 1 of treatment
3. The proportion of subjects with at least one incident of SpO_2 <90% for at least 30 seconds during TST on Day 1 of treatment

Secondary Endpoints (OSA Cohorts)

1. The AHI on Day 1 of treatment
2. The mean SpO_2 during TST on Day 1 and Day 8 of treatment
3. The percentage of TST during which the SpO_2 is <90%, <85% and <80% on Day 1 and Day 8 of treatment
4. The proportion of subjects with at least one incident of SpO2 <90% for at least 30 seconds during TST on Day 1 and Day 8 of treatment.

Exploratory Endpoints (HV and OSA Cohorts)

1. The mean SpO_2 during REM sleep, NREM and wake
2. The AHI during REM and NREM sleep
3. The AHI separately for adult and elderly subjects at all days assessed
4. The mean SpO_2 during TST separately for adult and elderly subjects at all days assessed

Pharmacokinetic Endpoint (HV and OSA Cohorts)

Lemborexant and metabolites M4, M9 and M10 plasma concentrations

Pharmacokinetic/Pharmacodynamic (Exposure-Response) Endpoint (HV and OSA Cohorts)

Correlations between plasma concentrations of lemborexant and select pharmacodynamic variables including AHI, mean SpO_2 during TST, and proportion of TST in which SpO_2 is <90%, <85% and <80% at all days assessed.

5.2 Study Subjects

5.2.1 Definitions of Analysis Sets

Analyses defined below are for each cohort separately.

Safety Analysis Set: Group of subjects who received study drug and have at least one postdose safety assessment.

Pharmacodynamic Analysis Set: The PD Analysis Set is the group of subjects who received at least 1 dose of study drug in each Treatment Period and who had sufficient PD data to derive at least 1 primary PD parameter.

Pharmacokinetic Analysis Set: Group of subjects who received at least 1 dose of lemborexant and who had sufficient PK data to derive at least 1 PK parameter.

5.2.2 Subject Disposition

The number of subjects screened and the number failing screening for each cohort (overall and by reason for failure) will be summarized. Screen failure data will be listed by cohort. The number of subjects randomized along with the number of subjects in each of the study populations will also be presented.

All disposition tables will be presented by cohort as follows:

The number of subjects completing the study will be presented. Subjects who prematurely terminated their participation in the study will be summarized by their primary reason for study termination. Other reasons for study drug and study terminations will also be summarized. These tabulations will be produced for all randomized subjects by treatment sequence.

The number of subjects screened and the number failing screening (overall and by reason for failure) will be summarized. Screen failure data will be listed. The number of subjects randomized along with the number of subjects in each of the study populations will also be presented.

The number of subjects completing the study will be presented. Subjects who prematurely terminated their participation in the study will be summarized by their primary reason for study termination. Other reasons for study drug and study terminations will also be summarized. These tabulations will be produced for all randomized subjects by treatment sequence.

The number and percentage of subjects will be summarized with the number in the FAS as the denominator, together with the number of subjects randomized but never dosed:

- Randomized but never dosed (only showing number of subjects)

- Completed treatment
- Prematurely discontinued treatment and the reasons for discontinuations
- Completed study
- Prematurely discontinued the study and the reasons for discontinuations

A listing will be provided for subjects who discontinued treatment or who discontinued study with reasons for discontinuation. A randomization listing will be provided with subjects ordered by randomization date.

5.2.3 Protocol Deviations

Protocol deviations, as specified by the monitor, will be categorized into major and minor deviations prior to unblinding and will be listed. Major protocol deviations will be presented as a listing by cohort.

No exploratory analyses is planned on subjects without important protocol violations since this is a safety study.

5.2.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set will be summarized for each sequence and overall using descriptive statistics for each cohort separately. Continuous demographic and baseline variables include age height, and weight; body mass index (BMI); categorical variables include sex, age group (<65, and >= 65 years), BMI group, race, and ethnicity.

MEDICAL HISTORY

The number (percentage) of subjects in the Safety Analysis Set reporting a history of any medical condition, as recorded on the CRF, will be presented as a listing by cohort. A subject data listing of medical and surgical history will be provided.

5.2.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) (Mar 2017 or latest version). The number (percentage) of subjects who took prior and concomitant medications will be presented as a listing by cohort. Prior medications will be defined as medications that stopped before the first dose of study drug. All medications will be presented in subject data listings.

Concomitant medications are defined as medications that (1) started before the first dose of study drug and are continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug to the last dose day plus 14 days. All medications will be presented in subject data listings.

5.2.6 Treatment Compliance

Compliance for the OSA Cohort each study drug will be calculated on the basis of the number of tablets dispensed, lost and returned, separately for each row of tablets and overall, for all randomized subjects.

$$\text{Compliance} = \frac{\text{Total number of tablets dispensed - total number of tablets returned or lost}}{\text{Number of tablets expected to be taken by the subject for the treatment period}} \times 100$$

Summaries will provide descriptive summary statistics and number (percentage) of subjects using the categories <80%, >= 80% to <= 100%, >100% to <= 120%, and > 120% for each treatment group.

Subjects in the HV Cohort will receive 1 dose of study medication per period while in clinic. Treatment compliance will not be calculated for this cohort.

5.3 Data Analysis General Considerations

5.3.1 Pooling of Centers

This study is a multicenter study across the United States, with approximately 10 sites. Due to the small sample size and the fact that this is a safety study, analysis will be based on pooling of data from different sites and there will be no by site analysis.

Pooling will be performed for each cohort independently based on each cohort's sites.

5.3.2 Adjustments for Covariates

Since this is a crossover study, there will be no adjustment for covariates like age, gender race, …etc. The model will include fixed effects for sequence, period, and treatment, and a random effect for subject within sequence.

5.3.3 Multiple Comparisons/Multiplicity

No multiplicity adjustments will be made. This is a phase I safety study.

5.3.4 Examination of Subgroups

Subgroup analysis of PD endpoints will be performed by age group (adults versus elderly) for the OSA Cohort.

5.3.5 Handling of Missing Data, Dropouts, and Outliers

In general, missing values due to subject discontinuation, missed or unusable assessments will not be imputed.

Incomplete/Missing data will not be imputed, unless otherwise specified; i.e., all missing values will remain as missing in all statistical analyses and listings, unless otherwise specified.

Outliers: No formal statistical analyses will be performed to detect and/or remedy the presence of statistical outliers.

5.3.6 Other Considerations

Individual subject data in the database will be presented in data listings.

5.3.7 Visit Window

All data will be presented using nominal visits as reported in the data. No additional derivation will be performed for analysis visit window.

5.4 Efficacy Analyses

No efficacy data will be recorded for this study.

5.4.1 Primary Pharmacodynamic Analyses

Analysis for the Primary Endpoint

HV Cohort: Mean SpO_2 during TST will be analyzed using a mixed effect model . The model will include fixed effects for sequence, period, and treatment, and a random effect for subject within sequence. The following will be presented: least squares (LS) means, difference in LS mean of lemborexant 10 mg and lemborexant 25 mg compared to placebo, a two-sided 90% CI (equivalent to a one-sided lower 95% CI) for the true mean difference (lemborexant − placebo) in SpO_2 and p-*v*alue. If the lower bound of the one-sided 95% CI of the treatment difference of SpO_2 is less than -5, this will provide evidence that the given dose of lemborexant does not result in a clinically significant decrease in SpO_2 compared to placebo.

OSA Cohort: AHI will be analyzed using a mixed effect model. The model will include fixed effects for sequence, period, and treatment, and a random effect for subject within sequence. The following will be presented: LS means, difference in LS mean of lemborexant 10 mg compared to placebo, a two-sided 90% CI (equivalent to a one-sided upper 95% CI) for the true mean difference (lemborexant − placebo) in AHI and *p*-value. If the upper bound of the one-sided 95% CI of the treatment difference of AHI is less than 5, this will provide evidence that the given dose of lemborexant does not result in a clinically significant increase in AHI with mild OSA compared with placebo.

A sensitivity analysis may also be performed on the primary endpoint where outliers are excluded. Other sensitivity analyses may be explored.

Plots of AHI and SpO_2 treatment difference data (both individual and LS Mean) will be used to explore the results.

5.4.2 Secondary Pharmacodynamic Analyses

Analysis for the Secondary Endpoints

The continuous secondary endpoints for both cohorts will be analyzed using the same model as the primary endpoint. Treatment comparison will be performed using contrasts.

The proportion of subjects with SpO2 <90% will be summarized using descriptive statistics. All analyses will be performed separately for each cohort.

5.4.3 Exploratory Analyses

Summaries and plots of all endpoints may be produced for appropriate subgroups (eg age group, sex, BMI, race) as deemed necessary.

5.5 Pharmacokinetic, Pharmacogenomic, and Other Biomarker Analyses

5.5.1 Pharmacokinetic Analyses

The Safety Analysis Set will be used for individual plasma concentration listings of lemborexant and its metabolites M4, M9, and M10. The PK Analysis Set will be used for summaries of plasma concentrations of lemborexant and its metabolites M4, M9, and M10, by dose.

5.5.2 Pharmacogenomic, and Other Biomarker Analyses

DNA samples will be collected and stored, and may be used to examine the role of genetic variability in absorption, distribution, metabolism, and excretion, or development of AEs. Variations in lemborexant exposure or AEs may be explored by correlation of single nucleotide polymorphisms with PK, safety, or PD data.

5.5.3 Pharmacokinetic/Pharmacodynamic (Exposure-Response) Analysis

The exposure-response (E-R) between plasma concentration of lemborexant after PSG, and selected PD parameters including but not limited to the respiratory safety variables, AHI, SpO_2 during TST, and the proportion of TST in which SpO2 is <90%, <85%, and <80%) will be explored graphically. Any emergent relationship may be followed using population model-based analysis. The potential effects of covariates (eg, age) on the E-R relationship may be explored. The PK analysis set will be used for these assessments. All analyses will be performed separately for each cohort.

5.6 Safety Analyses

Safety analyses will be performed on the Safety Analysis Set unless otherwise specified. Safety data, presented by treatment group, will be summarized on an “as treated” basis using descriptive statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables). Safety variables include treatment-emergent adverse events (TEAEs), clinical laboratory parameters, vital signs and 12-lead ECG results. Baseline for all safety analyses is defined as the last predose assessment prior to each periods’ dosing. Extent of Exposure

The extent of exposure (mean daily dose, cumulative dose, duration of exposure) to study drug will be summarized descriptively for lemborexant in the OSA Cohort. For the HV Cohort extent of exposure will be summarized by the number of subjects receiving each treatment.

Compliance for the OSA Cohort for lemborexant will be calculated on the basis of the number of tablets dispensed, lost, and returned, separately for each type (dose) of tablet. Summaries will provide descriptive summary statistics and number (percentage) of subjects below 80%, between 80% and 120%, and greater than 120%.

5.6.1 Adverse Events

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 20.1 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges during treatment, having been absent at pretreatment (Baseline) or

- Reemerged during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or

- Worsened in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings. AEs will be classified as TEAEs up to 14 days after the last study treatment.

An overview of the TEAEs will be summarized by treatment group, including the number and percentage of subjects who experience TEAEs, treatment-related TEAEs, severe TEAEs, TEAEs leading to death and discontinuation from study/study drug.

The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe). The number (percentage) of non-serious TEAEs with an incidence of greater than 5% will be summarized.

The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]). Treatment-related TEAEs include those events considered by the investigator to be related to study treatment.

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to death will be provided.

The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all SAEs will be provided.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT for each treatment. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

The number (percentage) of subjects with TEAEs of cataplexy that are characterized according to the customized MedDRA query PT as potential cataplexy-related events (Section 9.5.1.5 of the Protocol), or as seizure-related events will be summarized separately. Adjudicated events will also be presented separately.

5.6.2 Laboratory Values

Clinical laboratory values will be evaluated for each laboratory parameter by subject separately for each cohort. Abnormal laboratory values will be identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be included in the clinical study report for this study. Descriptive summary statistics (eg, mean, SD, median, minimum, maximum for continuous variables, and number and percentage for categorical variables) for the laboratory parameters and changes from baseline will be evaluated by treatment group and visit.

Laboratory test results will be assigned a low-normal-high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons will be based on 3 by 3 tables (shift tables) that, for a particular laboratory test, compare the Study Baseline LNH classification to the LNH classification at end of study/early termination, by treatment group.

Clinical laboratory results postbaseline will be evaluated for markedly abnormal values. A laboratory test will be considered markedly abnormal if the result worsens to meet Eisai grading criteria for laboratory values limit of Grade 2 or higher. If the Grade 2 limit is missing, the Grade 1 limit will be considered. Appendix 13.1 presents the Eisai grading criteria for laboratory values that were used to identify subjects with markedly abnormal laboratory values. For the incidence of markedly abnormal laboratory values, each subject may be counted once in the laboratory parameter value high and in the laboratory parameter low categories as applicable.

5.6.3 Vital Signs

Descriptive statistics for vital signs parameters (ie, diastolic and systolic BP, pulse, respiration rate, temperature) and weight, and changes from Baseline will be presented by treatment group and day relative to dosing, separately for each cohort.

Vital sign values will be listed. Clinically notable vital sign values will be identified on the listings as those above (H) or below (L) a clinically notable range (Table 1). Categorical analyses of subjects (number and percent) who fall outside the below clinically notable vital sign ranges will also be presented by treatment group and visit.

Table 1 Vital Sign Criteria

Variable	Criterion value[a]	Change relative to baseline[a]	Clinically notable range
Heart rate	>120 bpm	Increase of ≥ 15 bpm	H
	<50 bpm	Decrease of ≥15 bpm	L
Systolic BP	>180 mmHg	Increase of ≥20 mmHg	H
	<90 mmHg	Decrease of ≥20 mmHg	L
Diastolic BP	>105 mmHg	Increase of ≥15 mmHg	H
	<50 mmHg	Decrease of ≥15 mmHg	L

BP = blood pressure, bpm = beats per minute, H = high, L = low.

a. Clinically notable means that a value must meet the criterion value and must attain the specified magnitude of change relative to baseline.

5.6.4 Electrocardiograms

Descriptive statistics for ECG parameters and changes from Baseline will be presented separately for each cohort. Shift tables will present changes from Baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) by time point.

For each subject, the maximum observed corrected QT interval calculated using Fridericia's formula (QTcF), and the maximum prolongation from baseline in QTcF will be compiled. Categorical analyses of subjects (number and percent) with maximum observed QTcF values >450 msec, >480 msec, and >500 msec and maximum prolongations (from Baseline) in QTcF >30 msec and >60 msec will be presented by treatment group and by time point. Categorical analyses of subjects (number and percent) with maximum observed PR values >220 msec, and QRS values > 120 msec will be presented by treatment group and by time point.

6 INTERIM ANALYSES

No interim analyses are planned for this study.

7 CHANGES IN THE PLANNED ANALYSES

Not applicable.

8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

No missing data will be imputed.

9 PROGRAMMING SPECIFICATIONS

All analysis will be done separately for each cohort.

All pharmacodynamic and safety data will be presented using nominal timepoint as reported in the data. No additional derivation will be performed for analysis visit window.

The rules for programming derivations and dataset specifications are provided in separate documents.

10 STATISTICAL SOFTWARE

All statistical analyses will be performed using SAS v 9.3 or later.

11 MOCK TABLES, LISTINGS, AND GRAPHS

The study table, listing, and graph (TLG) shells will be provided in a separate document, which will show the content and format of all tables, listings, and graphs in detail. There will be two separate independent TLGs for the two cohorts.

12 REFERENCES

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13 APPENDICES

13.1 Sponsor's Grading for Determining Markedly Abnormal Laboratory Results

The following table of Sponsor's Grading for Laboratory Values is copied from the protocol, Appendix 1.

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<3.0 – 2.0×10^9/L <3000 – 2000/mm^3	<2.0 – 1.0×10^9/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <0.8 – 0.5×10^9/L	<500 – 200/mm^3 <0.5 – 0.2×10^9/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<1.5 – 1.0×10^9/L <1500 – 1000/mm^3	<1.0 – 0.5×10^9/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<75.0 – 50.0×10^9/L <75,000 – 50,000/mm^3	<50.0 – 25.0×10^9/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
				consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low (hypophosphatemia)	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

Based on Common Terminology Criteria for Adverse events (CTCAE) Version 4.0. Published: 28 May 2009 (v4.03: 14 Jun, 2010).
ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, , LLN = lower limit of normal, N/A = not applicable, ULN = upper limit of normal, WBC = white blood cell.

13.2 SAS Code Example for ANOVA

Proc Mixed can be used to analyze the crossover design data as follows:

```
proc mixed data=XXXX;
class sequence patient period treatment;
model Response= sequence patient period treatment /solution
ddfm=satterth;
random patient(sequence);
lsmeans drug / pdiff cl e;
run;
```

13.3 SAS Code Example for Proc Logistic

The following statements use the LOGISTIC procedure
to fit a two-way logit with interaction model for the effect of Treatment and AgeGroup, with Age as covariate. The categorical variables Treatment and Sex are declared in the CLASS statement.

proc logistic data=XXXX;

class Treatment AgeGroup;

model Binary_Response= Treatment Treatment*AgeGroup AgeGroup / expb;

run;

Programming Note: EXPB option displays the exponentiated values of the parameter estimates in the "Analysis of Maximum Likelihood Estimates" table for the logit model. These exponentiated values are the estimated odds ratios for the parameters.

SIGNATURE PAGE

Investigational Product Name: E2006/Lemborexant

SIGNATURES

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